REMARKS

Attached hereto is a marked-up version of the changes made to the Specification by the current amendment. The attached page is captioned "Version with markings to show changes made."

Status of the Claims

Claims 11 and 30-45 are pending in this application and claims 11, 31, 32, 34 and 36-43 are actively being prosecuted.

Reasons for this Supplemental Amendment and Response

Applicants, upon further consideration, are amending claim 11 to again recite "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity" which was deleted in the response of March 14, 2003. Entry of this amendment and consideration of the following arguments is hereby requested.

Rejection under 35 U.S.C. § 112, first paragraph, Enablement

Claims 11, 31-32, 34 and 36-43 have been rejected under 35 U.S.C. § 112, first paragraph, "because the specification, while being enabling for antibodies or fragments thereof which specifically bind SEQ ID NO:1 or immunogenic fragments thereof, does not reasonably provide enablement for antibodies or fragments thereof which specifically bind an isolated polypeptide comprising various naturally occurring "variants" of SEQ ID NO:1, as set forth in instant claim 11b (emphasis added)." (Office Action of December 16, 2002, page 4, § 12). Applicants traverse this rejection.

A. The Specification provides an enabling disclosure of the claimed antibodies

To fulfill the enablement requirement of 35 U.S.C. §112, first paragraph, the claimed invention must be described in the Specification in such as way as to enable one skilled in the relevant art to

which it pertains, or with which it is most nearly connected, to make and use the invention. In the present case, the Examiner is well aware that the relative skill of those in the art is very high and the amount of direction or guidance needed to be disclosed in the Specification **to make** and use the claimed antibodies as recited in amended claim 11 is minimal. Accordingly, it is submitted that the Specification does reasonably provide an adequate written description to **enable** the antibodies or fragments thereof which specifically bind SEQ ID NO:1 and various naturally occurring variants of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity as "now" claimed at the time of the filing of this application.

1. Variants of SEQ ID NO:1

The variants of SEQ ID NO:1 are defined in the Specification at, for example, at page 12, line 26 to page 13, line 4; page 14, lines 4-8. Polypeptide sequence variants are known by one of skill in the art to have amino acid substitutions which do not alter the function of the polypeptide. For example, a change of an amino acid residue to another at the extreme amino- or the carboxy-terminus of the sequence most likely will not alter the function of the polypeptide. The Specification defines specific structural domains related to PBPP proteins at page 13, lines 18-28; page 2, lines 4-13.

Moreover, claim 11 recites not only that the variant polypeptides have at least 90% sequence identity to, "the amino acid sequence of SEQ ID NO:1," but also have "***a naturally occurring amino acid sequence***," and said polypeptide has "phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequences of PBPP-1) and SEQ ID NO:2 (the polynucleotide sequence encoding PBPP-1), one of skill in the art would be able to routinely obtain "a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. For example:

The terms "stringent conditions"or "stringency", as used herein, refer to the conditions for hybridization as defined by the nucleic acid, salt, and temperature. These conditions are well known in the art and may be altered in order to identify or detect identical or related polynucleotide sequences. Numerous equivalent conditions comprising either low or high stringency depend on factors such as the length and nature of the sequence (DNA, RNA, base composition), nature of the target (DNA, RNA, base composition), milieu (in solution or immobilized on a solid substrate), concentration of salts and other components (e.g., formamide, dextran sulfate and/or polyethylene glycol), and temperature of the reactions (within a range from about 5°C below the melting temperature of the probe to about 20°C to 25°C below the melting temperature). One or more factors be may be varied to generate conditions of either low or high stringency different from, but equivalent to, the above listed conditions. (Specification at page 11, line 28 to page 12, line 9)

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding PBPP or closely related molecules, may be used to identify nucleic acid sequences which encode PBPP. The specificity of the probe, whether it is made from a highly specific region, e.g., 10 unique nucleotides in the 5' regulatory region, or a less specific region, e.g., especially in the 3' coding region, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low) will determine whether the probe identifies only naturally occurring sequences encoding PBPP, alleles, or related sequences. (Specification at page 35, line 30 to page 36, line 7)

Probes may also be used for the detection of related sequences, and should preferably contain at least 50% of the nucleotides from any of the PBPP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and derived from the nucleotide sequence of SEQ ID NO:2 or from genomic sequence including promoter, enhancer elements, and introns of the naturally occurring PBPP. (Specification at page 36, lines 8-12)

See also Example VI at page 48.

Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequences of SEQ ID NO:1. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. By adjusting the nature of the probe or nucleic acid (*i.e.*, non-conserved, conserved or highly conserved) and the conditions of hybridization (maximum, high, intermediate or low

stringency), one can obtain variant polynucleotides of SEQ ID NO:2 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:1 recited by the present claims.

A cDNA library could be constructed from any naturally occurring transcript as opposed to a "synthetically derived" transcript. One of skill in the art understands such sources to include for example, mRNA isolated from tissue samples, unperturbed tissue cultures and other such mRNA sources recovered from nature. Identification of specific cDNA libraries among the untold number of cDNA libraries made world-wide is unprecedented. The Specification does disclose examples of tissues in which PBPP was found to be expressed (see the Specification, for example, Figures 3A, 3B and 3C; p. 13, line 23 to p. 14, line 3). Therefore, one of ordinary skill in the art would understand those tissues that more likely than not, when used to construct a cDNA library could contain naturally-occurring variants of SEQ ID NO:1.

Clearly, given the high skill level of one of ordinary skill in the art and the teachings of the Specification, identification of 90% variants of SEQ ID NO:1 is considered routine experimentation. Accordingly, it is well within the skill of those in this art to identify those 90% variants of SEQ ID NO:1. Therefore, once said 90% variants are identified, isolated or made, the use of the variants to make antibodies to 90% variants of SEQ ID NO:1 requires neither extensive nor undue experimentation.

In addition, as set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 ***requires nothing more than objective enablement.*** [emphasis added] How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification would enable

one to make and use the 90% variants and immunogenic fragments of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established with respect to the 90% variants and immunogenic fragments of SEQ ID NO:1.

Accordingly, for all the above reasons, the claimed subject matter is described in the Specification in such a way that one skilled in the art can make and/or use the claimed invention. Therefore, reconsideration and withdrawal of this rejection to the claims are respectfully requested.

Rejection under 35 U.S.C. § 103(a), Obviousness

Each of the prior art rejections under 35 U.S.C. § 103(a) is based upon the combination of GenBank Accession No. AAB03214 (GI 1399101, Nussbaum, R.L.) with other references including: 1) Laxminarayan et al., (J. Biol. Chem. 1993; 268:4968-4974); 2) Palmer et al., (J. Biol. Chem. 1994; 269:3404-3410), and 3) Ramakrishnan et al. (U.S. Pat. No. 5,817,310). In particular, claims 11, 32, 34 and 36-38 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Laxminarayan et al. in view of GenBank Accession No. AAB03214; claims 11, 32, 34 and 39-41 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Palmer et al. in view of GenBank Accession No. AAB03214 and claims 31 and 42-43 stand rejected under 35 U.S.C. § 103(a) for allegedly being "unpatentable over Palmer et al., in view of GenBank Accession No. AAB03214," and further in view of Ramakrishnan et al. These rejections therefore are respectfully traversed.

Please note that claim 11 has been amended to include the recitation of **human** to more clearly identify that which Applicants have claimed as their invention. In addition, claim 11 b) is added to include recitation of a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity.

The claimed invention, as amended, is directed to an isolated ***human*** antibody which ***specifically binds*** to a polypeptide consisting of a polypeptide comprising the amino acid sequence of SEQ ID NO:1, a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity, and compositions comprising and methods directed to making and using said antibodies. By **"specifically binding"** to SEQ ID NO:1, the claimed antibody can bind

to a polypeptide consisting of SEQ ID NO:1 and a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity without cross-reactivity to other polypeptides even those which have extensive sequence identity to SEQ ID NO:1. Accordingly, so long as there are differences, even just one amino acid residue, between the amino acid sequences recited in claim 11 and those of the prior art, an antibody can be produced that can specifically bind to the polypeptides recited in claim 11 and not those of the prior art.

Even the Examiner recognizes this fact. The Examiner has relied previously on the Abaza et al. reference (J. Protein Chem. (1992) 11:433-444, of record). As taught by Abaza et al., a single amino acid substitution outside the antigenic site on a protein effect antibody binding. This provides scientific support of Applicants' assertion that so long as there are differences, even just one amino acid residue, between the amino acid sequences of claim 11 and those of the prior art, an antibody can be produced that can specifically bind to the polypeptides recited in claim 11 and not those of the prior art. Accordingly, given the amino acid differences between SEQ ID NO:1 and GenBank Accession No. AAB03214, one of skill in the art could produce an antibody ~~to SEQ ID NO:1~~ which binds to the polypeptides recited in claim 11 alone and without cross-reactivity to other polypeptides even those which have extensive sequence identity to SEQ ID NO:1.

Furthermore, Palmer et al. actually teach ***bovine*** antibodies and not **human** antibodies and therefore in view of GenBank Accession No. AAB03214, actually teaches away from the claimed invention. Hence, the cited art of GenBank Accession No. AAB03214, Palmer et al., Laxminarayan et al., and Ramakrishnan et al. could not have guided one of ordinary skill in the art to the claimed **human** antibodies which **specifically bind** to the polypeptides recited in claim 11. For at least the above reasons, Applicants believe withdrawal of the § 103 rejections are appropriate and are hereby requested.

Dock t No.: PF-0334-2 DIV

CONCLUSION

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 11 has been amended as follows:

11. (**Thrice Amended**) An isolated human antibody [which] that specifically binds to a polypeptide selected from the group consisting of:

a) [consisting of] a polypeptide comprising the amino acid sequence of SEQ ID NO:1, and

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity.